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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,009	03/28/2005	Constantin G. Ioannides	UTSC:711US	7673

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
10/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,009	IOANNIDES ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/28/08,4/2/08,7/20/07,9/7/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *6,7,10,12,13,16-19,24,25,27,30 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,9,11,14,15,20-23,26,28,29 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 September 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/24/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Request for Information Under 37 CFR 1.105.

DETAILED ACTION

1. Applicant's amendments and responses filed 7/28/08, 4/2/08 and 7/20/07 and amendment filed 9/7/04 are acknowledged and have been entered.

2. In view of the papers filed 8/15/05, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by the addition of Inventor George E. Peoples, Jr.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

3. Applicant's election without traverse of Group I and species of SEQ ID NO: 11 (KIFGSLA-iso-Phe-L), as well as "an increase in the antigen's ability to protect CTL's from activation induced cell death" as the species of "modulation of immunity" in Applicant's amendment and responses filed 7/20/07 and 7/28/08 is acknowledged. The Examiner notes that SEQ ID NO: 11 has the unnatural amino acid residue iso-Phe at position 8 (P8). Iso-Phe differs from Phe in that iso-Phe lacks the CH_2 group between the phenol ring and the peptide bond.

Claims 1-3, 8, 9, 11, 14, 15 and 28 read on the elected species.

Upon consideration of the prior art, examination has been extended to the species recited in instant claims 4, 5, 11, 20-23, 26, 27, 29 and 31.

Accordingly, claims 6, 7, 10, 12, 13, 16-19, 24, 25, 27, 30, and 32 (non-elected species) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 1-5, 8, 9, 11, 14, 15, 20-23, 26, 28, 29 and 31 are presently being examined.

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, for example in the Table legend on page 65 of the specification. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

5. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

6. The drawings are objected to because they contain handwritten text. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

7. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the Examiner on form PTO-892, they have not been considered.

8. The incorporation of *essential* material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the Applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

The attempt to incorporate subject matter into the instant application by reference to publications on pages 73-75 is improper because an application as filed must be complete in itself in order to comply with 35 USC 112. (Some of the references listed, *i.e.,* those on pages 72-75 of the specification, are "specifically incorporated herein by reference" "...to the extent that they provide exemplary procedural or other details supplementary to those set forth herein".)

An application for a patent when filed may incorporate "essential material" by reference to (1) a US patent or (2) a US patent application publication, which patent or patent publication does not itself incorporate such essential material by reference. "Essential material" is defined as that which is necessary to (1) provide a written description of the

claimed invention, and the manner and process of making and using it, in such full, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and set forth the best mode contemplated by the inventor of carrying out the invention, (2) describe the claimed invention in terms that particularly point out and distinctly claim the invention as required by the second paragraph of 35 USC 112, or (3) describe the structure, material or acts that correspond to a claimed means or step for performing a specified function as required by the sixth paragraph of 35 USC 112. In any application which is to issue as a US patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a US patent or application which itself incorporates "essential material" by reference, or (4) a foreign application. See *In re Fouche*, 439 F.2d 1237, 169 USPQ 429 (CCPA 1971).

Nonessential subject matter may be incorporated by reference to (1) patents or applications published by the US or foreign countries or regional patent offices, (2) prior and concurrently filed, commonly owned US applications, or (3) non-patent publications. Nonessential subject matter is subject matter referred to for purposes of indicating the background of the invention or illustrating the state of the art.

Applicant is invited to determine whether material incorporated by reference is essential or non-essential and amend the specification accordingly. (See MPEP 608.01(p)).

9. With regard to Applicant's IDS filed 4/24/06, references A1, A3 and A4 do not appear to be related to the subject matter of the disclosure of the instant application, *i.e.,* they are concerned with lead-free glass, molding and ceramics, respectively.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 9 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

a. Claim 9 is indefinite in the recitation of "wherein the first substitute amino acid reduces one-CH_2/CH_3 group on the side chain" because it is not clear what is meant, *i.e.,* if one CH_2 or one CH_3 group is meant or if CH_2CH_3 is meant.

b. Claim 14 is indefinite in the recitation of "further comprising determining the CTL epitope of the antigen" because it is not clear what is meant, *i.e.,* if the determining step precedes the method step recited in instant claim 1 upon which claim 14 depends. Claim 1 is drawn to a method for preparing a peptide antigen with modulated immunogenicity comprising substituting at least a first amino acid located in a CTL epitope with a first substitute amino acid having an extended or shortened side chain as

compared to the first amino acid. It appears that the CTL epitope has already been determined in claim 1. The instant specification does not disclose a definition for "determining."

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1, 4, 5, 11, 14, 20-22, 28 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Gillogly *et al* (FASEB J. 14: A147.18, 2000, Applicant's IDS reference "C19" in the Form 1449 filed 4/24/06) as evidenced by Castilleja *et al* (J. Immunol. 2002, 169: 3545-3554, IDS reference).

Gillogly *et al* teach making a panel of CTL peptide epitope "E75" (KIFGSLAFL) variants (from Her-2/neu breast and ovarian cancer associated antigen) with mutations directed to TCR contacts, and testing the variants for their ability to stimulate IFN-γ induction in healthy donors PBMC. Gillogly *et al* further teach "Of three E75 variants modified at presumed CDR3 contacts, which induced higher IFN-γ in PBMC than E75, one (F42= S5K)" (KIFG**K**LAFL) also activated cytolysis better than E75." Gillogly *et al* teach "Some of the P5 modified variants also induced higher levels of the anti-angiogenic chemokine IP-10 than E75." Gillogly *et al* also teach making a P8 variant of the E75 peptide, KIFSGSLA**K**L or "F46" that could also induce CTL.

Evidentiary reference Castilleja *et al* teach that the S5K variant is a weaker agonist than the unaltered peptide. Castilleja *et al* teach that replacement of the OH with an aminopropyl ($CH_2)_3$-NH_3 in variant S5K maintained a similar upward orientation of the side chain. Castilleja *et al* teach that S5K was a weaker stimulator than E75 for induction of lytic function. S5K-CTL survived longer than did CTL induced by E75, which became apoptotic after restimulation with the inducer (*i.e.*, the modulation of immunogenicity comprises an increase in the antigen's ability to protect CTLs from activation induced cell death). S5K-CTL also recognized E75 endogenously presented by the tumor by cytokine IFN-γ production and specific cytolysis (especially abstract).

During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. In re Prater 162 USPQ 541, 550 - 51 (CCPA 1969).

Claim 14 is included in the instant rejection because the art reference inherently teaches that the CTL epitope has been "determined." The instant specification does not disclose the definition of "determining" the CTL epitope of the antigen. Thus "determining" may encompass choosing a CTL epitope of an antigen of interest, wherein the epitope has already been identified by various procedures such as MHC binding algorithms, and *in vitro* and *in vivo* immunization with candidate epitopes. It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508.

14. Claims 1, 3, 4, 5, 8, 14, 15, 23 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Baker *et al* (Immunity, 2000, 13: 475-484, IDS reference).

Baker *et al* teach making analog peptides of the HTLV-1 peptide epitope LLFGYPVYV, said analogs being LLFGYAVYV and further position 6 (P6) analogs that utilize non-natural amino acid residues (N-ethyl glycine, N-methyl glycine and N-propyl alanine) to repair a packing defect in the interface between the P6A TCR and the P6A that effects TCR binding and signaling. Baker *et al* teach that the P6 N-ethyl glycine analog has a stimulatory activity and higher affinity greater than the wild-type unaltered peptide (see entire reference).

Claim 15 is included in this rejection because the peptides are modeled in the MHC class I binding groove.

In addition, the instant claims are included in this rejection because the P6 unaltered peptide is an agonist, whereas the P6-non-natural substituent peptides are weaker agonists.

During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. In re Prater 162 USPQ 541, 550 - 51 (CCPA 1969).

Claim 14 is included in the instant rejection because the art reference inherently teaches that the CTL epitope has been "determined." The instant specification does not disclose the definition of "determining" the CTL epitope of the antigen. Thus "determining" may encompass choosing a CTL epitope of an antigen of interest, wherein the epitope has already been identified by various procedures such as MHC binding algorithms, and *in vitro* and *in vivo* immunization with candidate epitopes.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508.

15. Claims 1, 2, 4, 5, 8, 14, 20-23, 26 and 29 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 01/36452 A2 (of record).

WO 01/36452 A2 teaches heteroclitic analogs of MHC class I binding peptide epitopes MAGE 3.112, CEA.691, MAGE2.157, HIVPol.476 and HIVPol.455. WO 01/36452 A2 teaches that these heteroclitic analogs produce either higher IFN-γ induction or IFN-γ and IL-10, and at lower levels than the wild type peptide, such analogs listed in Table 1, *i.e.,* for MAGE3.112, L5I and H7W, for CEA.691, I3M and V5H, for MAGE2.157 V5I and V5F, for HIVPol.476, K3H and K3L and for HIVPol.455, A7P. WO 01/36452 A2 also teaches heteroclitic analogs of p53.261, *i.e.,* F7L, G3H and G3D. The p53.261 heteroclitic peptide epitope analogs were more potent at inducing higher avidity CTL against the native wildtype epitope than the wildtype peptide itself. WO 01/36452 A2 also teaches heteroclitic analogs of the APRTLVYLL peptide epitope R3D, L5W and Y7P, and heteroclitic analogs of the KVFPYALINK peptide epitope F3H, Y5Q and L7K (see especially abstract, cover page, examples 2-11).

With regard to the inclusion of claims 2, 4, 5, 8, 23 and 26 in this rejection:

The L to I substitution in MAGE 3.112 is a substituted amino acid residue having the same base residue as the non-substituted amino acid residue (recited in instant claim 2).

The CEA.691M3 analog has a lengthened side chain in comparison to the non-substituted analog peptide epitope (recited in instant claim 5). The HIVPol.476 H3 and L3 peptide analogs have position 3 shortened side chains in comparison with the non-substituted peptide (recited in instant claim 8).

The side chains I and L variants have aliphatic side chains (recited in instant claim 4).

HIV peptides are from a viral antigen (recited in instant claim 23).

During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. In re Prater 162 USPQ 541, 550 - 51 (CCPA 1969).

Claim 14 is included in the instant rejection because the art reference inherently teaches that the CTL epitope has been "determined." The instant specification does not disclose the definition of "determining" the CTL epitope of the antigen. Thus "determining" may encompass choosing a CTL epitope of an antigen of interest, wherein the epitope has already been identified by various procedures such as MHC binding algorithms, and *in vitro* and *in vivo* immunization with candidate epitopes.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508.

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 1, 4, 5, 11, 14, 15, 20-22, 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over in view of Gillogly *et al* (FASEB J. 14: A147.18, 2000, Applicant's IDS reference "C19" in the Form 1449 filed 4/24/06) in view of Fisk *et al* (J. Exp. Med. 1995, 181: 2109-2117, IDS reference) and Madden *et al* (Cell. 1993, 75: 693-708, IDS reference).

Gillogly *et al* teach making a panel of CTL peptide epitope "E75" (KIFGSLAFL) variants with mutations directed to TCR contacts, and testing the variants for their ability to stimulate IFN-γ induction in healthy donors PBMC. Gillogly *et al* further teach "Of three E75 variants modified at presumed CDR3 contacts, which induced higher IFN-γ in PBMC than E75, one (F42= S5K)" (KIFG**K**LAFL) also activated cytolysis better than E75." teach "Some of the P5 modified variants also induced higher levels of the anti-angiogenic chemokine IP-10 than E75." Gillogly *et al* also teach making a P8 variant of the E75 peptide, KIFSGSLA**K**L or "F46" that could also induce CTL. Gillogly *et al* teach "TCR-directed tumor Ag variants may become components of tumor vaccines to prime non-responding cancer patients."

Gillogly *et al* do not teach wherein the method comprises determining the CTL epitope of the antigen by a method of evaluating peptides with MHC class I binding anchor motifs for their ability to be recognized by antigen-specific or ovarian-tumor specific CTL lines, nor modeling the CTL epitope while bound in the MHC class I binding groove.

Fisk *et al* teach identifying the E75 epitope from tumor antigen HER-2 by making synthetic peptides representative of subsequences in the Her-2 protein that possess MHC class I HLA-A2.1 binding anchor motifs, followed by evaluation of their ability to be recognized by ovarian-tumor specific CTL (see entire reference, especially abstract).

Madden *et al* teach complexes of five peptides bound to the human class I MHC molecule HLA-A2 have been studied by X-ray crystallography, that the peptide termini and the second and C-terminal anchor side chains are bound similarly in all five cases, but the main chain and side chain conformations for each peptide are strikingly different

in the center of the binding site and these differences are accessible to direct TCR recognition. Madden *et al* further teach that although fixed at its ends, the structure of an MHC-bound peptide appears to be a highly complex function of its entire sequence, potentially sensitive to even small sequence differences (especially abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have identified an epitope or epitopes as taught by Fisk *et al* for other tumor antigens, to have designed a panel of TCR contact variants as taught by Gillogly *et al* and to have modeled the variants in the MHC class I binding groove as taught by Madden *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to design heteroclitic peptide variants of a tumor-associated antigen wherein the variant amino acid residues and the overall conformation of the peptide is permissive for appropriate TCR contacts. In addition, one of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to study the conformation of the peptide and its side chains in relationship to TCR contact area in correlation with the modification in immunogenicity associated with the variant peptide.

18. This Office Action has an attached requirement for information under 37 CFR 1.105. A complete reply to this Office Action must include a complete reply to the attached requirement for information. The time period for reply to the attached requirement coincides with the time period for reply to this Office Action.

19. Claim 1 is objected to because of the following informalitiy: there is a spelling error in claim 1, *i.e.*, "a least" at line 2 should be "at least." Appropriate correction is required.

20. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Eileen B. O'Hara, can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
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October 22, 2008

/Michael Szperka/
Primary Examiner, Art Unit 1644